June 6, 2018

Lt. Cdr. Brian Andrews-Shigaki
Office Warfighter Performance S&T Dept
875 N. Randolph St.
Arlington, VA 22203-1995

Subject: Interim Technical Report with SF298 by the National Marrow Donor Program®

Reference: Grant N00014-17-1-2850 between the Office of Naval Research and the National Marrow Donor Program

Dear Lt. Cdr. Andrews-Shigaki,

In accordance with the requirements of the referenced Office of Naval Research Grant, the National Marrow Donor Program (NMDP) hereby submits the required Interim Technical Report for the period of January 01, 2018 through May 31, 2018.

Should you have any questions regarding the performance activity of under this Grant, you may contact our Chief Medical Officer – Dennis Confer, MD directly at 763-406-3425.

Please direct any contractual questions pertaining to the Grant to me at 763-406-3401 or to npoland@nmdp.org.

Sincerely,

Nancy R. Poland, M.A.
Contracts and Compliance Manager

c: Patricia Woodhouse – ONR-Chicago
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Martin Maiers – NMDP

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14. ABSTRACT
1. Contingency Prepardness: Collect information from transplant centers, build awareness of the Transplant Center Contingency Planning Committee and educate the transplant community about the critical importance of establishing a nationwide contingency response plan.

2. Rapid Identification of Matched Donors: Increase operational efficiencies that accelerate the search process and increase patient access are key to preparedness in a contingency event.

3. Immunogenetic Studies: Increase understanding of the immunologic factors important in HSC transplantation.

4. Clinical Research in Transplantation: Create a platform that facilitates multicenter collaboration and data management.

15. SUBJECT TERMS
Research in HLA Typing, Hematopoietic Stem Cell Transplantation and Clinical Studies to Improve Outcomes

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Grant Award N00014-17-1-2850

DEVELOPMENT OF MEDICAL TECHNOLOGY FOR CONTINGENCY RESPONSE TO MARROW TOXIC AGENTS

INTERIM RESEARCH PERFORMANCE REPORT

SUBMITTED JUNE 6, 2018

Office of Naval Research

And

The National Marrow Donor Program®

500 5th St N

Minneapolis, MN 55401

I. Heading

PI: Dennis L. Confer, M.D.

National Marrow Donor Program

N00014-17-1-2850

Development of Medical Technology for Contingency Response to Marrow Toxic Agents

II. Scientific and Technical Objectives

The main objective of this grant is to develop, test and mature the ability of the National Marrow Donor Program® (NMDP) to address contingency events wherein civilian or military personnel are exposed to marrow toxic agents, primarily ionizing radiation or chemical weapons containing nitrogen mustard. An accident, a military incident, or terrorist act in which a number of individuals are exposed to marrow toxic agents will result in injuries from mild to lethal. Casualties will be triaged by first responders, and those with major marrow injuries who may ultimately be candidates for hematopoietic cell transplantation (HCT) will need to be identified. HCT donor identification activities will be initiated for all potential HCT candidates. NMDP-approved transplant centers will provide a uniform and consistent clinical foundation for receiving, evaluating and caring for casualties. NMDP coordinating center will orchestrate the process to rapidly identify the best available donor or cord blood unit for each patient utilizing its state-of-the-art communication infrastructure, sample repository, laboratory network, and human leukocyte antigen (HLA) expertise. NMDP's on-going immunobiologic and clinical research activities promote studies to advance the science and technology of HCT to improve outcomes and quality of life for the patients.

III. Approach

A. Contingency Preparedness

HCT teams are uniquely positioned to care for the casualties of marrow toxic injuries. The NMDP manages a network of centers that work in concert to facilitate unrelated HCT. The Radiation Injury Treatment Network (RITN), comprised of a subset of NMDP's network centers, is dedicated to radiological disaster preparedness activities and develops procedures for response to marrow toxic mass casualty incidents.

B. Immunogenetic Studies in Transplantation

Improving strategies to avoid and manage complications due to graft alloreactivity is essential to improve the outcomes of HCT. Research efforts are focused on strategies to maximize disease control while minimizing the toxicity related to alloreactivity in HCT.

C. Clinical Research in Transplantation

Clinical research creates a platform that facilitates multi-center collaboration and data management to address issues important for managing radiation exposure casualties. Advancing the already robust research capabilities of the NMDP network will facilitate a coordinated and effective contingency response.

IV. Updates

A. Contingency Preparedness

Maintain the Radiation Injury Treatment Network (RITN) to prepare for the care of patients resulting from a hematopoietic toxic event.

Project: Triage Guidelines for Cytokine Administration Following a Radiological Disaster

1. The workgroup that will create the guidelines has been formed with members representing:
    a. Hematology/Oncology Adult Care
    b. Hematology/Oncology Pediatric Care
    c. Rad/Oncology
    d. Health Physics
    e. Emergency Medicine
    f. Burn Care
    g. State Public Health
    h. Federal Public Health
    i. Emergency Management.
2. The group has developed draft guidelines and continues to refine the document for adult and pediatric guidance.
3. The project has adopted a broader scope to include the creation of a toolkit of materials from existing sources to support the guidelines.

Project: Hematologic Laboratory Surge Network Exercise and Plan Development

1. The project has assessed the lab surge needs within the distant communities and determined that the potential surge in this area will not overwhelm the community.
2. During this review, the local surge was identified as a significant risk that needs to be addressed.
3. Following this direction, the project has begun to establish a coalition of laboratory networks and collaborating with John's Hopkins, as well as the Biomedical Advanced Research and Development Authority to create a lab surge plan for the communities proximal to the incident.

Project: Local Public Health Radiological Preparedness Gap Review and Tool Development Identification

1. The National Association of County and City Health Officials (NACCHO) has held multiple conference calls with leaders within their organization to identify the areas of concern.
2. During the NACCHO annual Preparedness Summit conference, an in person workshop was held to review the key areas where gaps exist and prioritized their need for resolution.
3. NACCHO is developing a report at this time.

Project: Radiological Disaster Webinar Training Series for Inexperienced Public Health Staff

1. The Association of State and Territorial Health Officials (ASTHO) was selected to work on this project.
2. ASTHO modified the project to create training courses instead of recording webinars.
3. ASTHO has posted an RFP for the course development, selected a vendor and has begun recording subject matter experts in the area to use in the course development.

B. Immunogenetic Studies in Transplantation

HLA mismatches may differ in their impact on transplant outcome, therefore, it is important to identify and quantify the influence of specific HLA mismatches. In contingency situations, it will not be possible to delay transplant until a perfectly matched donor can be found.

Project: Evaluation and identification of whole genome donor-recipient pair variation and donor-specific DNA methylation patterns that affect HCT outcomes

1. A contract has been established with Medical College of Wisconsin's (MCW) Genomic Sciences and Precision Medicine Center (GSPMC) for whole genome sequencing (WGS) and epigenetic sequencing for transplants.
2. A study has been proposed focusing on relapse in patients transplanted for Myelodysplastic syndromes (MDS) and who carry wild type for TP53, RAS pathway and JAK2 mutations.
3. The pilot cohort of 188 samples has been selected and sent for sequencing.
    a. 47 donor/recipient pairs (cases) from transplants where the patient developed disease relapse post HCT.

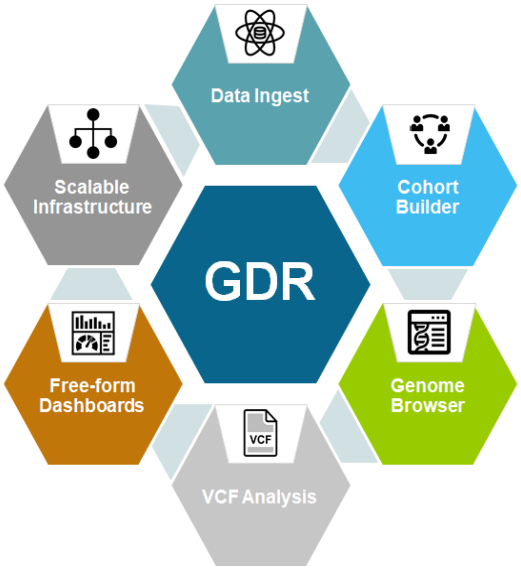
b. 47 donor/recipient pairs (controls) from transplants patients who had at least the same duration of follow up post HCT but remain in remission

4. The laboratory at the GSPMC facility has started to perform DNA methylation sequencing and long insert whole genome sequencing on all 94 samples.
5. Weekly collaborative meetings have taken place between researchers from both Minneapolis and Milwaukee Center for International Blood and Marrow Transplant Research (CIBMTR) campuses to track the progress of the typing and develop the statistical analysis approach.
6. A contract has been established with a vendor to assist in building the technology for a "Genetic Data Repository" system for storage and data analysis. A three-month project has been completed with a buildout of a functional data storage and analytics platform (section "Genomic Data Repository" (GDR) below).

Genomic Data Repository

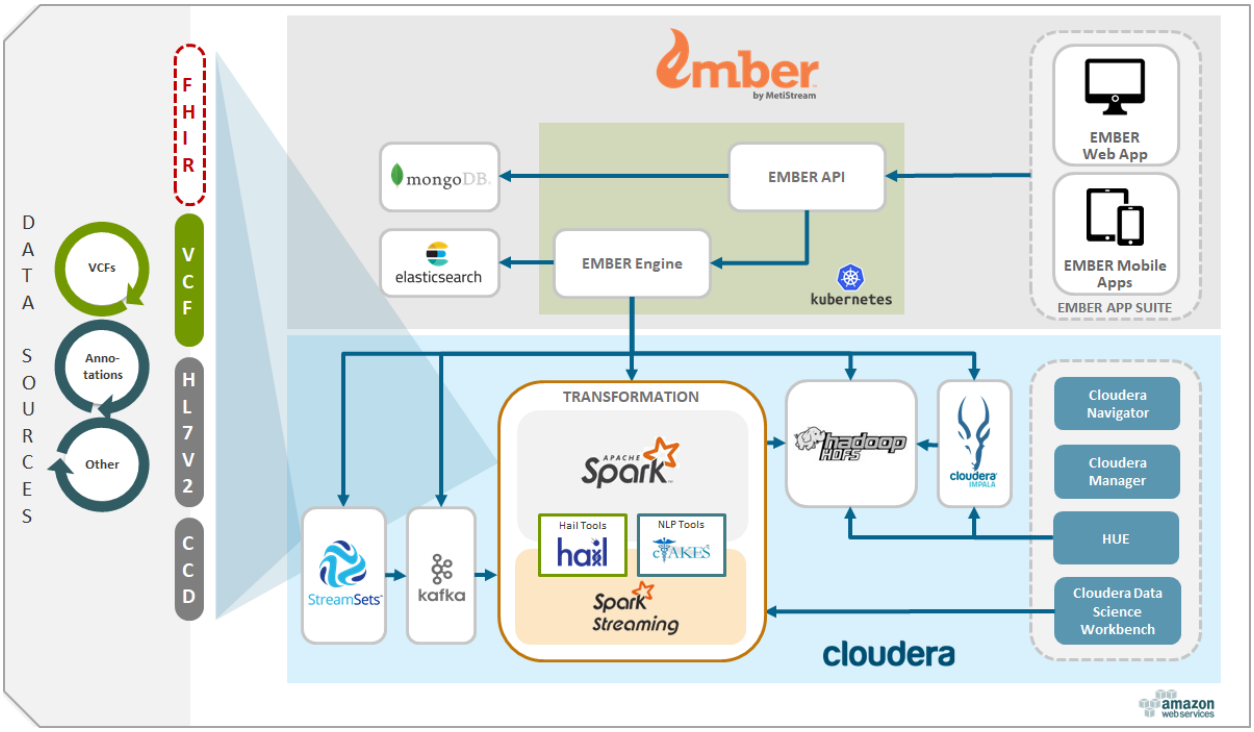
A first phase of development was completed on a GDR that can provide the scalable storage, repository management, user collaboration, and enhanced analytic capabilities for genomic variant call files. In order to provide the GDR capability, a vendor was selected and development was initiated on an existing healthcare analytics platform.

A three-month effort has concluded which has resulted in the establishment of a functional product with several functional components in place for the intake of genomic data and analysis. During the next year, this system will be used to store results of the MDS project funded under this grant and other genomic typing projects that have been completed prior to the development of the GDR.



The solution architecture for the GDR (see diagram) is based on open-source technologies and scalable cloud-based infrastructure and leverages an existing healthcare analytics tool with capabilities of integrating genomic and clinical data using clinical informatics exchange

standards (Health Level 7 – version 2 and Health Level 7 – Fast Healthcare Interoperability Resources (HL7-FHIR)). See section C: Clinical Research in Transplantation for more activity relating to HL7-FHIR.



C. Clinical Research in Transplantation

Clinical research in transplantation improves transplant outcomes and supports preparedness for a contingency response.

Project: Patient Report Outcomes (PRO). Incorporating patient reported quality of life (QOL) assessments into CIBMTR data collection

CIBMTR's Electronic Patient Reported Outcomes (ePRO) system integrates Qualtrics (a subscription software for collecting and analyzing data) online surveys with Patient-Reported Outcomes Measurement Information System (PROMIS®) computer adapted test measures and Salesforce customer relationship management (CRM) to administer quality of life and other patient reported outcomes with follow-up support by the Survey Research Group (SRG).

Accomplishments:

Successfully deployed Phases 1 & 2 of the ePRO system in production in mid-May. This includes:

1. Integration of Qualtrics online surveys with PROMIS API
    a. Installed PROMIS application programming interface (API) on NMDP servers. This includes database of all current PROMIS measures and algorithm for selecting questions via Computer Adaptive Test methodology and for calculating scores.
    b. Connected Qualtrics to the PROMIS API with a bridge API that helps PROMIS and Qualtrics track the status of a given patient's survey.
    c. Successfully tested.
2. Integration of Salesforce and Qualtrics Online surveys
    a. Installed Salesforce app to Qualtrics.
    b. Implemented mechanism to send contacts from Salesforce to Qualtrics for generating and tracking unique survey links.
    c. Implemented mechanism to record completed time points in Salesforce when a patient completes their Patient Reported Outcomes (PRO) in Qualtrics – generates 'completed time point' contact attempt; closes open activities to prevent further outreach by SRG; marks time point as complete.
3. Enhancement of Salesforce application to be compliant with HIPAA and NMDP security standards.

a. Okta Single-Sign-On, with multi-factor authentication in Qualtrics and Salesforce. Okta is a company that allow users to log into a variety of systems using one centralized process.

b. Encryption of personally identifiable information (PII) and protected health information (PHI) data in Salesforce.

c. System hardening in Qualtrics and Salesforce.

d. In depth review of Qualtrics and Salesforce with security partner to ensure compliance with HIPAA, 21 CFR part 11, and NMDP security standards.

Remaining scope to be delivered:

1. Launch the pilot study, enrolling initial patients by the beginning of June.
2. Store PRO data and scores in the Integrated Data Warehouse for the pilot study.
3. Review and enhance system monitoring capabilities for when servers are down or there are other issues with the APIs or other system components.
4. Build backlog of enhancements to Salesforce or Qualtrics for future development.

Project: Development of a Regenerative Medicine Registry

No work has started yet on this project. We are dependent on some key stakeholders to arrange meetings and get started on forms development.

Project: Enhancing Existing IRB software application(s) to streamline NMDP single IRB Processes

NMDP began to investigate the possibility of purchasing an Institutional Review Board (IRB) management software solution from an external vendor. Such a solution would not only streamline NMDP single IRB processes, but would serve as a complete IRB management system for NMDP's human research protection program. Utilizing an external vendor could possibly save money and effort.

- Software requirements were outlined and potential vendors were identified.
- An RFP/RFQ was released to the vendors.
- Following Q&A with vendors, vendors submitted responses to the RFP/RFQ.
- Vendor demonstrations of solutions occurred.
- Finalists were chosen.

Project: Support for developing HL7 Fast Healthcare Interoperability Resources (FHIR) tools to enhance interoperability of AGNIS® with Electronic Medical Records

The tremendous scientific value of CIBMTR research is threatened by reliance on manual data entry through web-based forms at most HCT centers. CIBMTR created A Growable Network Information System **(**AGNIS) to overcome this challenge. While powerful, adoption of AGNIS

at a broader range of transplant centers has been limited because of burdens associated with data mapping and/or a lack of available resources with sufficient technical expertise. Because AGNIS replicates the FormsNet User Interface forms, any change to information being captured requires new form definitions, resulting in new mappings to local data elements. This process is inefficient. Beginning in the fall of 2017, we embarked on a project to incorporate a new messaging interface to AGNIS using healthcare informatics standards that embrace modern approaches to data exchange – HL7 FHIR.

Accomplishments:

1. The initial infrastructure has been established with the development of the needed hardware (servers).
2. A draft (client) application has been created to communicate with Epic's Electronic Health Records sandbox (testing) server.
3. An initial proof of concept data exchange with the Epic testing server using HL7 FHIR's Patient Resource (structured data set pertaining to patients) was developed, and patient resource data started being exchanged in May within test environments.
4. Patient Resource data has been used to search for existing CIBMTR Recipient IDs (CRIDs) and assign a new CRID. New CRID has been stored into the CIBMTR FHIR server. This was the first step in ensuring the prevention of duplicate patient records.
5. Demonstrated initial FHIR client interface application at FHIR Connectathon, which is an international meeting where developers exchange data and test connections.

Remaining scope to be delivered:

1. Consult FHIR SMEs to ensure conformance with established FHIR standards.
2. Collaborate with partner transplant centers to identify necessary enhancements to the draft client application.
3. Introduction of security layers for FHIR server interaction.
4. Introduction of security layers for interactions with CIBMTR services.
5. Upload genomic resource to Epic FHIR sandbox for retrieval by our tool using alternate search criteria.
6. Enhancement of automated search scripts to allow additional FHIR Resources to be used in search criteria or retrieved from the Epic Sandbox.
7. Introduction of a mapping script to ease the burden of implementation for partner transplant centers.
8. Development of a draft Implementation Guide (a set of rules about how FHIR resources are used when exchanging data with CIBMTR).

V. Major Problems/Issues (if any)

No major problems encountered to date.

VI. Technology Transfer

No technology transfer to report.

VII. Foreign Collaborations and Supported Foreign Nationals

NMDP has no sub awards with nor is it collaborating with any foreign entity or foreign national under this grant.

VIII. Productivity

1. Refereed Journal Articles – None to report
2. Non-Refereed Significant Publications – None to report
3. Books or Chapters – None to report
4. Technical Reports – None to report
5. Workshop and conference abstracts and presentations – None to report
6. Patents – None to report
7. Awards/Honors – None to report

IX. Award Participants

Employee name	**Employee name**
Andrew Brown	Josh Mandel
Angela Kummerow	Julia Tkachenko
Ann Jakubowski	Julia Udell
Bill Burgess	Kirt Schaper
Bronwen Shaw	Lloyd McKenzie
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